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Three-Component Thieno[2,3-b]indole Synthesis from Indoles, Alkenes or Alkynes and Sulfur Powder under Metal-Free Conditions

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Abstract: A Bronsted acid promoted three-component synthesis of substituted thieno[2,3-b]indole has been developed starting from indoles, alkenes or alkynes, and sulfur powder. N,N-Dimethylformamide plays an important role to convert the starting materials into the fused products. Various functional groups attached to substrates were well tolerated to afford the corresponding products in moderate to good yields under very simple reaction conditions.

Keywords: Thieno[2,3-b]indole; Sulfur powder; Threecomponent reaction; Metal-free; C-H functionalization

Indole and its derivatives widely exist in a variety of naturally occurring products and are extremely important in medicinal chemistry for their biological activities.^[1] In particular, the thieno[2,3-b]indoles are valued for their great potential as antifungal agent.^[2] Thienodolin is a natural product isolated from Streptomyces albogriseolus and exhibits plantgrowth regulatory properties.^[3] The substituted thieno[2,3-b]indoles are useful for the treatment of epilepsy, neurological diseases such as Parkinson's disease and pain.^[4] Additionally, thieno[2,3derivatives *b*]indole show great potential applications in organic electroluminescent devices and polymer conductors.^[5]

There are few methods for the synthesis of thieno[2,3-b]indoles in the literature, including deoxygenative cyclization of 2 - (2 nitrophenyl)thiophene in refluxing triethyl phosphate,^[6] oxidative cyclization of indolin-2thiones,^[7] radical or palladium-catalyzed cyclization 3-(2-bromoindol-3yl)acrylonitriles,^[8] of condensation of 3-unsubstituted indolin-2-thione.^[9] intramolecular NH/CH-coupling in benzo[b]thiophenes.^[10] condensation of 1alkylisatins and acetylated (hetero)arenes,^[11] AlCl₃-

catalyzed recyclization of $2 - (2 - 1)^{-1}$ nitrocyabatophenyl)furanes,^[12] and among others.^[13] However, all the aforementioned synthetic methods use functionalized indoles, furans, isatins and thiophenes, which require several steps to be prepared. In view of the concerns about the influences of trace metals on human consumption drugs and the efficiency of organic electronic devices, the development of metal-free catalytic processes for the direct functionalization of indoles is of great interest and importance.^[14] Efficient methods for the construction of substituted thieno[2,3-b]indoles from simple indoles and other readily available starting materials under metal-free conditions are highly desirable.

Our previous work



Scheme 1. Synthesis of indole-fused heterocycles from indoles

The direct C-H functionalization of hetero C-H bond is one of the most popular research topics in organic

chemistry since this method can provide a more direct synthetic route by avoiding substrate prefunctionalization.^[15] Among them, indole C-H bond functionalization has attracted considerable interest since the indole motif is a privileged functional group for pharmaceutical drugs and agrochemicals as well as electronic materials.^[16] Recently, we and others have developed various approaches for the synthesis of heterocycles indole fused via C-H bond functionalization. For example, in 2015, we reported a palladium-catalyzed benzothieno[2,3-b]indole formation using sulfur powder as the sulfur source via dehydrative-dehydrogenative double C-H sulfuration under an oxygen atmosphere (Scheme 1, a).^[17] In 2016, we developed a concise synthesis of pyrazolo[1,5a]indole derivatives by copper-catalyzed aerobic oxygenation and cyclization of indoles with oxime acetates (Scheme 1, b).^[18] Very recently, we described an efficient one-pot two-step indole-to-carbazole strategy from cheap and readily available indoles, ketones, and alkenes with oxygen as the sole oxidant (Scheme 1, c).^[19] As our continuing efforts on the construction of fused heterocycles via indole C-H bond functionalization, herein, we developed an one-pot three-component synthesis of substituted thieno[2,3b]indoles from readily available indoles, alkenes or alkynes, and sulfur powder under metal-free conditions (Scheme 1, d).

To obtain optimized reaction conditions for the direct cyclization, 1-methylindole (1a),phenylacetylene (2a) and sulfur powder were initially used as the standard substrates under different conditions (Table 1). When the reaction was performed using formic acid as the acid at 150 °C in DMF for 16 h, the desired annulation product 3a was obtained in 34% yield (Table 1, entry 1). This result encouraged us to test a series of organic acids such as HOAc, TFA, TsOH, MsOH, TfOH, PivOH, and BzOH (Table 1, entries 2-8). Among them, HOAc increased the yield of 3a to 70% (Table 1, Several inorganic acids were also entry 2). investigated for this transformation (Table 1, entries 9-12), of which hydrochloric acid (6 M) showed the best efficiency to give the corresponding product **3a** in 86% yield (Table 1, entry 9). Decreasing the reaction temperature or the concentration of hydrochloric acid both slightly decreased the reaction yield (Table 1, entries 13-15). No desired product 3a was observed when the reaction was carried out in the absence of DMF (Table 1, entry 16 and Table S1 in the Supporting Information).

Table 1. Optimization of reaction conditions.^[a]



Entry	Acid	Yield (%) ^[b]
1	formic acid	34
2	HOAc	70
3	TFA	30
4	TsOH	58
5	MsOH	16
6	TfOH	43
7	PivOH	58
8	benzoic acid	58
9	HCl (6 mol/L) (0.1 mL)	86
10	HNO ₃ (6 mol/L) (0.1 mL)	43
11	H ₂ SO ₄ (3 mol/L) (0.1 mL)	59
12	H ₃ PO ₄ (2 mol/L) (0.1 mL)	80
13	HCl (3 mol/L) (0.1 mL)	64
14	HCl (1 mol/L) (0.1 mL)	46
15 ^[c]	HCl (6 mol/L) (0.1 mL)	59
16 ^[d]	HCl (6 mol/L) (0.1 mL)	0

^[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), S_8 (0.125 mmol), acid (5 equiv.), DMF (0.3 mL), 150 °C,16 h, under air atmosphere.

^[b] GC yield based on **1a**.

^[c] 130 °C.

^[d] Without DMF.

Under the optimized conditions, various indoles and alkynes were explored as the substrates, and the results are summarized in Table 2. A series of para-substituted phenylacetylene smoothly reacted with 1a and sulfur powder to give thieno[2,3-b]indoles in moderate to good yields (**3aa-3aj**). The structure of **3aa** was further confirmed by X-ray crystallography (Fig. S1 in ESI). It should be noted that cleavage of the C-halogen bond was not observed as determined by GC-MS analysis. The reaction yield decreased dramatically when 1chloro-2-ethynylbenzene was used as the substrate (3ak), probably because of the highly steric hindrance. The reaction yield decreased obviously when using aliphatic alkynes as the substrate, such as 1-octyne (2m)and 3,3-dimethylbut-1-yne (2n), which were coupled with **1a** to give the desired products in 31% and 47% yields, respectively. Upon using diphenyl acetylene (20), 3ao was obtained in 34% yields. Furthermore, indoles bearing various substituents could smoothly couple with phenylacetylene and sulfur powder. Firstly, the influence of various substituents at the C-5 position was evaluated (3ba-3ga). In general, the reactions proceeded smoothly to give the corresponding products in moderate to good yields. Functional groups such as fluoro, chloro, bromo and even iodo were all compatible under the optimized reaction conditions. Good yields were observed when the substituents were located at the C-6 position and C-7 position of 1methyl-1H-indole (3ha-3ja). To our delight, free indole (1k) could also couple with 2a and the yield was as good as 1-methylindole. Meanwhile, 1-ethyl-1Hindole (11) and 1-isopropyl-1*H*-indole (1m) were also

suitable substrates for this kind of reaction to give the corresponding products (**3la-3oa**) in good yields.

Table 2. Substrate scope with respect to the indoles and alkynes. $\ensuremath{^{[a]}}$



^[a] *Conditions*: **1** (0.2 mmol), **2** (0.4 mmol), S_8 (0.125 mmol), HCl (6 M, 0.1 mL), DMF (0.3 mL), 150 °C, 16 h, under air atmosphere. Isolated yield based on **1**.

Furthermore, we examined the reactions between indoles and various substituted alkenes (Table 3). We re-optimized the reaction conditions and were delighted to find that the reactions could be smoothly performed in HCl:HOAc (v/v=3:7)as the combinational acid, which afforded the desired product 3aa in 76% yield. In general, reactions between 1methyl-indole and the styrene derivatives bearing electron-donating groups such as CH₃ or OCH₃, or halogens such as F, Cl, or Br on the aromatic ring all gave the desired products in moderate to good yields (3ab, 3af-3aj). The positions of the substituents on the phenyl ring significantly affected the reaction yields, and 3ak was obtained in only 30% yield when 1chloro-2-vinylbenzene was used. Subsequently, a wide range of substituted indoles were screened to couple with styrene in moderate to good yields, regardless of the functional groups at the C-5, C-6, or C-7 position. A broad range of functional groups on the indole ring such as methyl, methoxy, fluoro, chloro and bromo were tolerated well. Notably, unprotected 1H-indole participated well in this protocol to provide the corresponding product **3ka** in 74% yield. We further tested this method with *N*-ethylindole and 1-isopropyl-1*H*-indole, and the reaction proceeded smoothly to provide the desired products in good yields (**3la-3na**).





^[a] *Conditions*: **1** (0.2 mmol), **4** (0.4 mmol), S_8 (0.125 mmol), HCl (6 M, 0.03 mL), HOAc (0.07 mL) DMF (0.3 mL), 150 °C, 16 h, under air atmosphere. Isolated yield based on **1**.

Control experiments were carried out to gain preliminary insight into the reaction mechanism. Treatment of 2a or 4a with sulfur powder under standard conditions without 1-methyl-indole (1a) for 16 h gave *N*,*N*-dimethyl-2-phenylethanethioamide (**5a**) in 55% and 45% yields, respectively (Scheme 2, a and b). Trace amount of the desired product was obtained when 1-methyl-3-styryl-1H-indole (6a) was treated with sulfur powder (Scheme 2, c). Further treatment of N,N-dimethyl-2-phenylethanethioamide (5a) with 1methyl-indole (1a) afforded the desired product 3aa in 45% yield. No desired product was observed when the reaction was carried out in the absence of S₈, and the product 3aa could be gained in 77% yield when 3 equiv. of sulfur powder was added to the reaction (Scheme 2, e). The product **3aa** could be gained in 77% yield when using 2-phenylthiirane (7a) as the substrate with 1methyl-indole (1a). Based on these observations, a plausible mechanism to rationalize this transformation is illustrated in Scheme 3. Initially, intermediate A is generated from 2a or 4a with DMF and sulfur powder (Willgerodt-Kindler reaction)^[20] or from **5a** via resonated procedure ^[21] Then, 1-methyl-indole (1a) reacts with intermediate A to afford an intermediate B,

which can be further converted into the desired product (**3aa**) under acidic conditions. DMF plays an imprtant role to convert the starting materials into the final product.



Scheme 2. Control experiments.



Scheme 3. Proposed reaction pathway.

In summary, we have developed a simple and efficient method for the synthesis of thieno[2,3b]indole from indoles, alkenes or alkynes, and sulfur powder under metal-free conditions. DMF plays an important role to convert the starting materials into the fused products. Various functional groups were well tolerated under the optimized reaction conditions. This method affords an efficient and general approach for the synthesis of biologically important substituted thieno[2,3-b]indole from readily available strarting materials under simple reaction conditions.

Experimental Section

General procedure

1-Methyl-1*H*-indole (25.0 μ L, 0.2 mmol), phenylacetylene (44 μ L, 0.4 mmol) and sulfur powder (32.0 mg, 1.0 mmol) were added to a 20 mL reaction vessel. HCl (6 M, 0.1 mL) and DMF (0.3 mL) were then added by syringe. The sealed reaction vessel was stirred at 150 °C under air for 16 h. After cooling to room temperature, the reaction was diluted with ethyl acetate (5 mL) and washed with saturated salt water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate for three times. The combined organic layer was dried over sodium sulfate, the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 300:1) to yield the desired product **3aa** as white solid (40.0 mg, 76% yield), mp 136-138 °C. R_f = 0.60 (100:1 petroleum ether/EtOAc).

CCDC-1501644 contains supplementary the crystallographic data for this paper. These data can be obtained The Cambridge free of charge from Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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